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A one-pot synthesis of 3-arylglutaric anhydrides by reaction of ketene with aromatic aldehydes and ketones

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ABSTRACT

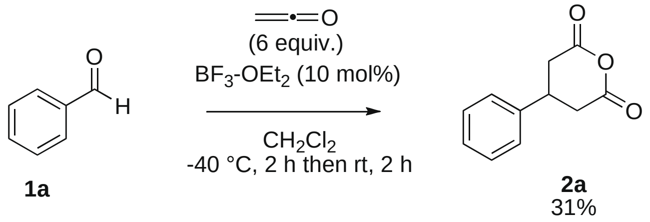
Aromatic aldehydes and ketones react with ketene under Lewis acid catalysis to produce β-lactones, which in situ react with another molecule of ketene to produce 3-arylglutaric anhydrides. The mechanism, scope, and limitation of this one-pot synthesis of 3-substituted glutaric anhydrides are discussed.

Desymmetrization of *meso*- and prochiral compounds is a powerful approach in asymmetric synthesis.[1] 3-Aryglutaric anhydrides are particularly useful starting compounds in this approach.[2–5] For example, asymmetric alcoholysis of 3-(*p*-chlorophenyl)glutaric anhydride by Novozyme 435 affords the glutaric half ester enantioselectively which serves as chiral building block for (*R*)-Baclofen, a selective GABA$_B$ receptor agonist.[2] Asymmetric methanolysis of 3-aryglutaric anhydrides using cinchona-based catalysts also affords the glutaric half ester enantioselectively which is the key intermediate for $\alpha_v\beta_3$ receptor antagonist for the treatment of osteoporosis.[3]

3-Aryglutaric acids have been generally synthesized by condensation of arylaldehydes with two molecules of ethyl acetoacetate followed by deacetylation and hydrolysis of ester groups by strong base.[6] Recently, a one-pot synthesis of 3-aryglutaric acids has been reported.[7] In this method, bis-isoxazole derivatives formed from 3,5-dimethyl-4-nitroisoxazole and arylaldehydes are oxidized in situ to the dicarboxylic acids by $KMnO_4$. Glutaric anhydrides are obtained by treatment of glutaric acids with acetic anhydride. Here, we report the first one-pot synthesis of 3-aryl- or 3-alkyl-3-arylglutaric anhydrides by reaction of ketene with benzaldehydes or acetophenones under a Lewis acid catalysis.

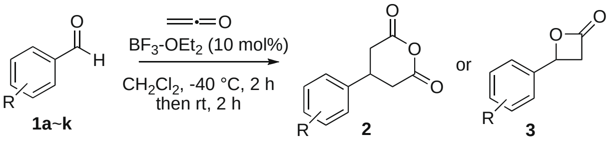
It has been well known that ketene reacts with carbonyl compounds to produce β-lactones.[8–10] When 6 mol equiv of ketene generated from acetone by ketene lamp[11] was introduced over 2 h into a solution of benzaldehyde **1a** and BF_3 etherate (10 mol %) in dichloromethane at −40 °C and the whole was stirred at room temperature for 2 h, 3-phenylglutaric anhydride **2a** was obtained in 31% yield (Scheme 1).[12,13]

We have studied the generality of this new reaction of ketene with benzaldehydes. The results for reaction of *p*- and *o*-substituted benzaldehydes with ketene under the above-mentioned condition are summarized in Table 1. *p*-Methoxy-, *p*-chloro-, and *p*-bromo-benzaldehydes **1b–d** afforded the corresponding 3-arylglutaric anhydrides **2b–d** in 39–61% yields, while



Scheme 1.

Table 1
Reaction of ketene with benzaldehydes



Entry	R	Product			
		No	Yield (%)	No.	Yield (%)
1	H	**2a**	31	–	–
2	*p*-OMe	**2b**	50	–	–
3	*p*-Cl	**2c**	39	–	–
4	*p*-Br	**2d**	61	–	–
5	*p*-CF_3	–	–	**3e**	86
6	*p*-CN	–	–	**3f**	82
7	*p*-NO_2	–	–	**3g**	88
8	*o*-OMe	**2h**	23	–	–
9	*o*-NO_2	–	–	**3i**	62
10	*o*-Br	–	–	**3j**	81
11	*o*-Cl	–	–	**3k**	49

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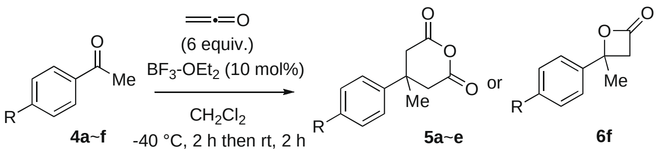
p-trifluoromethyl-, *p*-cyano-, and *p*-nitro-benzaldehydes **1e**–**g** produced the corresponding β-lactones **3e**–**g** in 82–86% yields.

o-Methoxybenzaldehyde **1h** also afforded the glutaric anhydride **2h** in 23% yield, while *o*-nitro, *o*-bromo-, and *o*-chloro-benzaldehydes afforded the corresponding β-lactones **3i**, **3j**, and **3k** in 62%, 81%, and 49% yields, respectively.

This indicates that benzaldehydes without electron-withdrawing substituent generally produce the corresponding glutaric anhydrides, while those with strong electron-withdrawing substituent produce only β-lactones.

The reactions of ketene with acetophenone and the *p*-substituted derivatives **4a**–**f** were also examined. The results are summarized in Table 2. Acetophenone **4a** gave 3-methyl-3-phenylglutaric anhydride **5a** in 40% yield. *p*-Substituted acetophenones **4b**–**e** also afforded the corresponding 3,3-disubstituted glutaric anhydrides **5b**–**e** in 25–55% yields, while *p*-nitroacetophenone **4f** gave β-lactone **6f** in 71% yield.

Table 2
Reaction of ketene with acetophenones

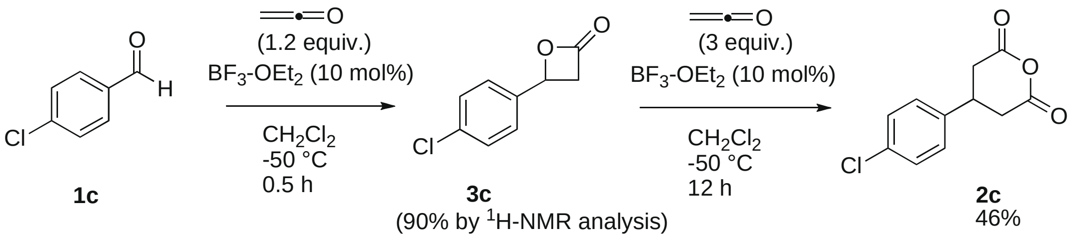


Entry	R	Product			
		No.	Yield (%)	No.	Yield (%)
1	H	**5a**	40	–	–
2	OMe	**5b**	42	–	–
3	Me	**5c**	55	–	–
4	Br	**5d**	32	–	–
5	Cl	**5e**	25	–	–
6	NO_2	–	–	**6f**	71

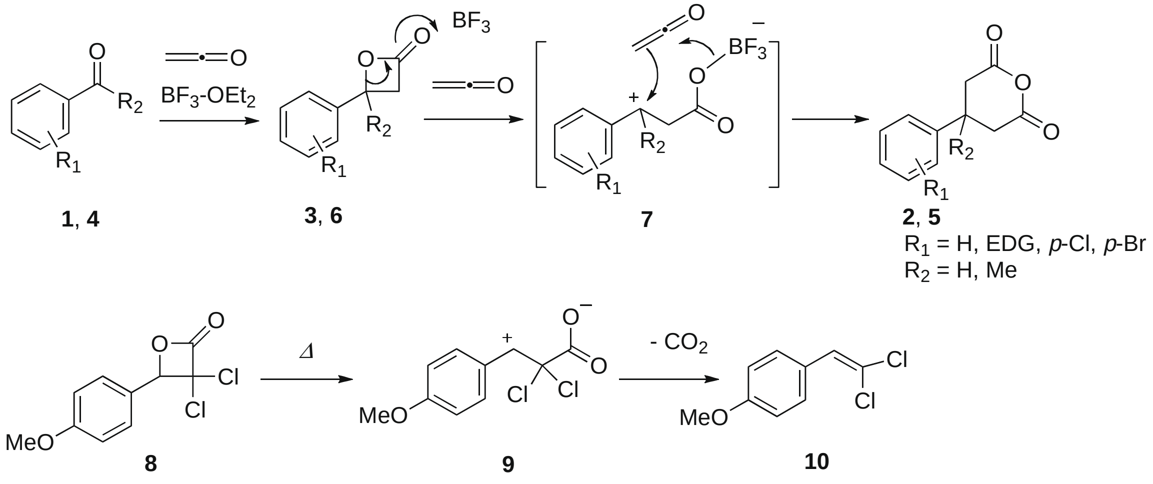
We have studied the mechanism of this new reaction of ketene with carbonyl compounds. It is reasonable to assume that ketene reacts with carbonyl compounds to form β-lactones as initial products, to which another molecule of ketene adds by BF_3 catalyst.

Reaction of *p*-chlorobenzaldehyde **1c** with 1.2 equiv of ketene in the presence of BF_3 etherate (10 mol %) gave β-lactone **3c** in ca. 90% yield as revealed by ^{1}H NMR analysis of the reaction mixture. This lactone was isolated by silica gel column chromatography and was treated with 3 mol equiv of ketene under BF_3 etherate catalyst (10 mol %) to produce the glutaric anhydride **2c** in 46% yield, clearly showing the intermediary of β-lactones for 3-substituted glutaric anhydrides (Scheme 2).

A possible mechanism for the formation of 3-substituted glutaric anhydrides is illustrated in Scheme 3. β-Lactones **3** and **6** are formed from the carbonyl compounds. β-Lactones with strong electron-withdrawing substituents such as trifluoromethyl, cyano, and nitro groups on the aromatic ring are stable enough under the reaction condition and they are obtained in good yields. β-Lactones without electron-withdrawing group on the aromatic ring are ring-opened by the Lewis acid catalyst to form dipolar intermediates **7**, which are intercepted by another molecule of ketene to form glutaric anhydrides **2** and **5**. Halogens on aromatic ring have an electron-withdrawing inductive effect and an electron-donating resonance effect. The formation of glutaric anhydrides **2c**,**d** from the corresponding *p*-halophenyl lactones is rationalized by the resonance effect. In the *o*-halophenyl lactones **3j**,**k**, the inductive effect of nearby halogen operates strongly to disturb the formation of benzylic cation **7**.



Scheme 2.



Scheme 3.

It should be noted that previous attempts to intercept a dipolar intermediate **9** derived from 4-aryl-3,3-dichlorooxetan-2-one **8** with vinyl ether or methyl acrylate under heating were unsuccessful; the reactions exclusively afforded styrene derivative **10**.[14]

In conclusion, we have found that ketene reacts with aromatic aldehydes and ketones under BF_3 catalyst to give β-lactones, which further react with another molecule of ketene to produce 3-aryl- and 3-alkyl-3-arylglutaric anhydrides. This reaction is very attractive for the synthesis of 3-substituted glutaric anhydrides that are starting materials for the preparation of useful compounds. The reaction uses one-pot procedure and has a high degree of atom economy. Since ketene is economically produced on an industrial scale, this method would be applicable to a large-scale production.

Acknowledgment

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12. *General procedure for reaction of ketene with benzaldehydes and acetophenones*: To a solution of benzaldehyde (531 mg, 5 mmol) and BF_3–OEt_2 (32 μL, 0.25 mmol) in dichloromethane (40 mL), ketene (30 mmol) was introduced over 45 min at −40 °C and the mixture was stirred at −40 °C for 2 h and at room temperature for 2 h. Water (40 mL) was added to the reaction mixture and the whole was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and condensed under reduced pressure to give oily residue. Purification by silica gel column chromatography (hexane–AcOEt, 5:1) gave **2a** (228 mg, 31%) as colorless needles of mp 105 °C (recrystallized from hexane–AcOEt). ^{1}H NMR ($CDCl_3$) δ: 7.40 (2H, t, J = 7.4 Hz), 7.34 (1H, t, J = 7.4 Hz), 7.20 (2H, d, J = 7.4 Hz), 3.40–3.46 (1H, m), 3.12 (2H, dd, J = 17.0, 4.0 Hz), 2.87 (2H, dd, J = 17.0, 12.0 Hz).
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